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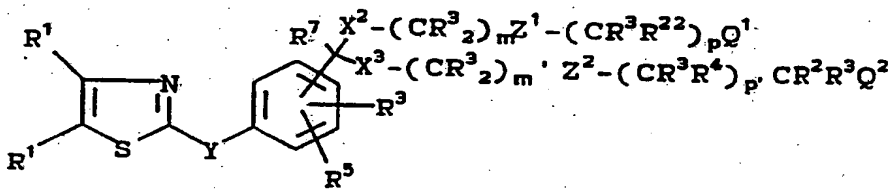

(I)

(57) Abstract

Compounds having formula (I) are antagonists of the actions of leukotrienes. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

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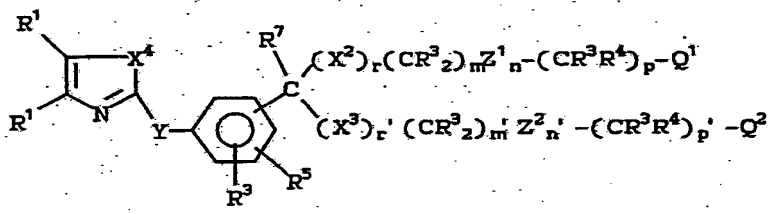
THIAZOLE-SUBSTITUTED BENZYL ALCOHOLS AS LEUKOTRIENE ANTAGONISTS

BACKGROUND OF THE INVENTION

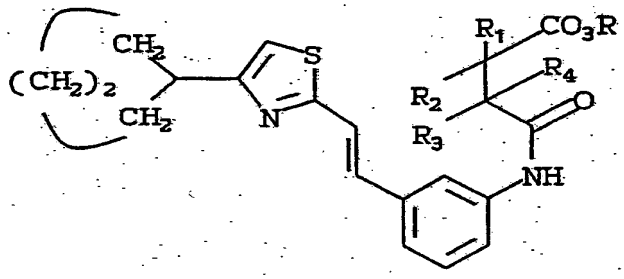
The leukotrienes constitute a group of locally acting hormones, produced in living systems from arachidonic acid. The major leukotrienes are Leukotriene B_4 (abbreviated at LTB_4), LTC_4, LTD_4 and LTE_4. The biosynthesis of these leukotrienes begins with the action of the enzyme 5-lipoxygenase on arachidonic acid to produce the epoxide known as leukotriene A_4 (LTA_4), which is converted to the other leukotrienes by subsequent enzymatic steps. Further details of the biosynthesis as well as the metabolism of the leukotrienes are to be found in the book Leukotrienes and Lipoxygenases, ed. J. Rokach,

Elsevier, Amsterdam (1989). The actions of the leukotrienes in living systems and their contribution to various diseases states are also discussed in the book by Rokach.

U.S. Patent 4,962,117 (Oct. 9, 1990) and European patent application 355,353 (July 7, 1989) disclose structures of leukotriene antagonists which differ from the present compounds, most notably in the absence of the benzyl alcohol. The structures of the compounds disclosed in the above patent applications are shown below.



U.S. P. 4,962,117



EP 355,353

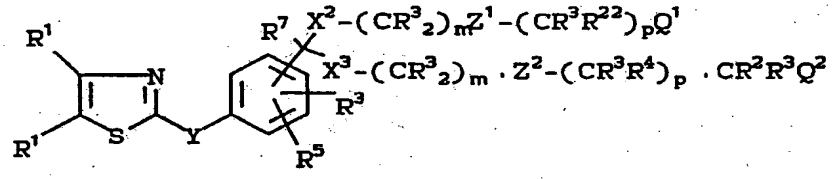
SUMMARY OF THE INVENTION

The present invention relates to thiazole-substituted benzyl alcohols having activity as leukotriene antagonists, to methods for their preparation, and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

Because of their activity as leukotriene antagonists, the compounds of the present invention are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are best realized by Formula I:



I

wherein:

R^1 is H, halogen, CN, lower alkyl, cyloalkyl, polyhalo lower alkyl, lower alkoxy lower alkyl, lower alkoxy, lower alkylthio lower alkyl, substituted or unsubstituted phenylthio lower alkyl, substituted or unsubstituted phenyl, benzyl, pyridyl, thiazolyl, oxazolyl, furanyl or thienyl, or adjacent R^1's and the carbons through which they are attached may form a saturated ring of 5 to 7 carbon atoms;

R^2 is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2CF_3$, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, or two R^2 groups joined to the same carbon may form a saturated ring of up to 8 members containing 0 to 2 heteroatoms chosen from O, S, and N;

R^3 is H or R^2;

CR^3R^{22} may be the radical of a standard amino acid;

R^4 is halogen, $-NO_2$, $-CN$, $-OR^3$, $-SR^3$, NR^3R^3, $NR^3C(O)R^7$, or R^3;

R^5 is H, halogen, $-NO_2$, $-N_3$, $-CN$, $-SR^2$, $-NR^3R^3$, $-OR^3$, lower alkyl, or $-C(O)R^3$;

R^6 is $-(CH_2)_s-C(R^7R^7)-(CH_2)_s-R^8$ or $-CH_2C(O)NR^{12}R^{12}$;

R^7 is H or lower alkyl;

R^8 is A) a monocyclic or bicyclic heterocyclic radical containing from 3 to 12 nuclear carbon atoms and 1 or 2 nuclear heteroatoms selected from N, S or O and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or B) the radical $W-R^9$;

R^9 is contains up to 20 carbon atoms and is (1) an alkyl group or (2) an alkylcarbonyl group of an organic acyclic or monocyclic carboxylic acid containing not more than 1 heteroatom in the ring;

R^{10} is $-SR^{11}$, $-OR^{12}$, or $-NR^{12}R^{12}$;

R^{11} is lower alkyl, $-C(O)R^{14}$, unsubstituted phenyl, or unsubstituted benzyl;

R^{12} is H, R^{11}, or two R^{12} groups joined to the same N may form a saturated ring of 5 or 6 members containing up to two heteroatoms chosen from O, S, and N;

R^{13} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;

R^{14} is H or R^{13};

R^{15} is R^3 or halogen;

R^{16} is H, lower alkyl, or OH;

R^{17} is lower alkyl, lower alkenyl, lower alkynyl, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;

R^{18} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;

R^{19} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;

R^{20} is H, lower alkyl, substituted or unsubstituted phenyl, benzyl, phenethyl, or pyridinyl, or two R^{20} groups joined to the same N may form a saturated ring of 5 or 6 members containing one to two heteroatoms chosen from O, S, and or N;

R^{21} is H or R^{17};

R^{22} is R^4, CHR^7OR^3, or CHR^7SR^2;

m and m' are independently 0-8;

p and p' are independently 0-8;

m + p is 1-10 when X^2 is O, S, S(O), or $S(O)_2$;

m + p is 0-10 when X^2 is CR^3R^{16} or a bond;

m' + p' is 0-10;

s is 0-3;

Q^1 is $-C(O)OR^3$, 1H (or 2H)-tetrazol-5-yl, $-C(O)OR^6$, $-C(O)NHS(O)_2R^{13}$, -CN, $-C(O)NR^{12}R^{12}$, $NR^{21}S(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{21}C(O)R^{18}$, $OC(O)NR^{12}R^{12}$, $-C(O)R^{19}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{12}R^{12}$, $-NO_2$, $NR^{21}C(O)OR^{17}$, $-C(NR^{12}R^{12})=NR^{12}$, or $-C(R^{13})=NOH$; or if Q^1 is C(O)OH and R^{22} is -OH, -SH, CHR^7OH or $-NHR^3$, then Q^1 and R^{22} and the carbons through which they are attached may form a heterocyclic ring by loss of water;

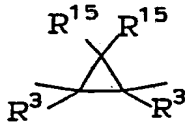
Q^2 is OR^3;

W is O, S, or NR^3;

X^1 is O, S, $-S(O)-$, $-S(O)_2-$, $-N(R^3)-$, or $-CR^3R^3-$;

X^2 and X^3 are independently O, S, S(O), $S(O)_2$, CR^3R^{16}, or a bond;

Y is $-CR^3=CR^3-$, $-C\equiv C-$, $-CR^3R^3-X^1-$, $-X^1-CR^3R^3-$, $-CR^3R^3-X^1-CR^3R^3-$, $-C(O)-$, $-NR^3C(O)-$, $-C(O)NR^3-$, O, S, NR^3, or



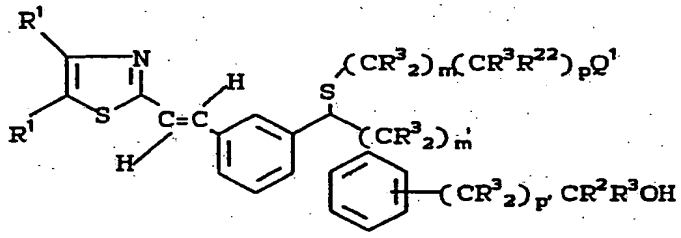
;

Z^1 and Z^2 are independently $-HET(-R^3-R^5)-$ or a bond;

HET is the diradical of a benzene, a pyridine, a furan or a thiophene;

or a pharmaceutically acceptable salt thereof.

More preferred compounds of Formula I are represented by Formula Ia:



Ia

wherein:

R^{22} is R^3, $-CH_2OR^3$, or $-CH_2SR^2$;

Q^1 is $-C(O)OH$, 1H(or 2H)-tetrazol-5-yl, $-C(O)NHS(O)_2R^{13}$, $-C(O)NR^{12}R^{12}$, or $-NHS(O)_2R^{13}$;

m' is 2 or 3;

p' is 0 or 1;

m + p is 1-5; and

the remaining definitions are as in Formula I; or a pharmaceutically acceptable salt thereof.

The following abbreviations have the indicated meanings:

AIBN = 2,2'-azobis(isobutyronitrile)
Py = 2-, 3-, or 4-pyridyl
Fu = 2- or 3-furanyl
Et = ethyl
Me = methyl
Bz = benzyl
Ph = phenyl
t-Bu = tert-butyl
i-Pr = isopropyl
n-Pr = normal propyl
c-Hex = cyclohexyl
c-Pr = cyclopropyl
c- = cyclo
Ac = acetyl
Tz = tetrazol-5-yl
Th = 2- or 3-thienyl

C_3H_5 = allyl
c-Pen = cyclopentyl
c-Bu = cyclobutyl
PPTS = pyridinium p-toluene sulfonate
phe = benzenediyl
NBS = N-bromosuccinimide
NCS = N-chlorosuccinimide
pye = pyridinediyl
PTSA = p-toluenesulfonic acid
fur = furandiyl
r.t. = room temperature
thio = thiophenediyl
DHP = 4H-2,3-dihydropyran
THP = tetrahydropyran

The terms alkyl, alkenyl, and alkynyl mean linear and branched structures and combinations thereof.

The term "alkyl" includes "lower alkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, and the like.

The term "polyhalo" means one or more hydrogen atoms are replaced by halogen atoms.

The term "lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, and the like.

The term "cycloalkyl" refers to a hydrocarbon, containing one or more rings of from 3 to 12 carbon atoms, with the hydrocarbon having up to

a total of 20 carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cycloheptyl, aldamantyl, cyclododecylmethyl, 2-ethyl-1-bicyclo[4.4.0]decyl, and the like.

The term "alkenyl" includes "lower alkenyl" and means alkenyl groups of 2 to 20 carbon atoms. Examples of alkenyl groups include allyl, 5-decen-1-yl, 2-dodecen-1-yl, and the like.

"Lower alkenyl" means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Cycloalkenyl" means alkenyl groups of 3 to 20 carbon atoms, which include a ring of 3 to 12 carbon atoms, and in which the alkenyl double bond may be located anywhere in the structure. Examples of cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-vinyladamant-1-yl, 5-methylenedodec-1-yl, and the like.

The term "alkynyl" includes "lower alkynyl" and means alkynyl groups of 2 to 20 carbon atoms. Examples of alkynyl groups are ethynyl, 2-pentadecyn-1-yl, 1-eicosyn-1-yl, and the like.

"Lower alkynyl" means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, and the like.

The term "cycloalkynyl" means alkynyl groups of 5 to 20 carbon atoms, which include a ring of 3 to 20 carbon atoms. The alkynyl triple bond may be located anywhere in the group, with the proviso that

if it is within a ring, such a ring must be of 10 members or greater. Examples of cycloalkynyl are cyclododecyn-3-yl, 3-cyclohexyl-1-propyn-1-yl, and the like.

The term "lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

The term "lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

The term "lower alkylsulfonyl" means alkylsulfonyl groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkylsulfonyl groups are methylsulfonyl, 2-butylsulfonyl, cyclohexylmethyl-sulfonyl, etc. By way of illustration, the 2-butylsulfonyl group signifies $-S(O)_2CH(CH_3)CH_2CH_3$.

"Alkylcarbonyl" includes "lower alkylcarbonyl" and means alkylcarbonyl groups of 1 to 20 carbon atoms of a straight, branched, or cyclic configuration. Examples of alkylcarbonyl groups are 2-methylbutanoyl, octadecanoyl, 11-cyclohexyl-undecanoyl and the like. Thus, the 11-cyclohexyl-undecanoyl group is c-Hex-$(CH_2)_{10}$-C(O)-.

The term "lower alkylcarbonyl" means alkylcarbonyl groups of from 1 to 8 carbon atoms of a straight, branched, or cyclic configuration.

Examples of lower alkylcarbonyl groups are formyl, 2-methylbutanoyl, cyclohexylacetyl, etc. By way of illustration, the 2-methylbutanoyl groups signifies $-C(O)CH(CH_3)CH_2CH_3$.

Substituted-phenyl, -benzyl, -2-phenethyl, or -pyridinyl means that the aromatic ring carries 1 or 2 substituents selected from lower alkyl, R^{10}, NO_2, SCF_3, halogen, $-C(O)R^7$, $-C(O)R^{10}$, CN, CF_3, and Tz.

Halogen includes F, Cl, Br, and I.

It is intended that the definitions of any substituent (e.g., R^1, R^2, R^{10}, etc.) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, $-NR^{12}R^{12}$ represents -NHH, $-NHCH_3$, $-NHC_6H_5$, etc.

The saturated rings formed when two R^1 groups join through two adjacent carbon atoms include c-pentane, c-hexane, c-heptane, c-octane, c-nonane, and c-decane.

The saturated rings formed when two R^2 groups join through C include c-propane, c-pentane, c-hexane, c-octane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, thiopyran, dioxan, piperidine, morpholine, thiomorpholine, piperazine, and their N-lower alkyl analogs.

The heterocycles formed when two R^{12} or R^{20} groups join through N include pyrrolidine, piperidine, morpholine, thiamorpholine, piperazine, and N-methylpiperazine.

When Q^1 and R^{22} and the carbons through which they are attached form a ring, the rings thus formed include lactones, lactams, and thiolactones.

The prodrug esters of Q^1 (i.e., when $Q^1 = CO_2R^6$) are intended to include the esters such as are described by Saari et al., J. Med. Chem., 21, No. 8,

746-753 (1978), Sakamoto et al., Chem. Pharm. Bull., 32, No. 6, 2241-2248 (1984), and Bundgaard et al., J. Med. Chem., 30, No. 3, 451-454 (1987).

Within the definition of R^8, some representative monocyclic or bicyclic heterocyclic radicals are:

2,5-dioxo-1-pyrrolidinyl,
(3-Pyridinylcarbonyl)amino,
1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl,
1,3-dihydro-2H-isoindol-2-yl,
2,4-imidazolinedion-1-yl,
2,6-piperidinedion-1-yl,
2-imidazolyl,
2-oxo-1,3-dioxolen-4-yl,
piperidin-1-yl,
morpholin-1-yl, and
piperazin-1-yl.

"Standard amino acid", the radical of which may be CR^3R^{22}, means the following amino acids: alanine, asparagine, aspartic acid, arginine, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. See F.H.C. Crick, Symposium of the Society of Experimental Biology, 12, 140 (1958).

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and

resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof. Optically active (R) and (S) isomers may be resolved using conventional techniques.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol,

ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The ability of the compounds of Formula I to antagonize the actions of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a human subject. This antagonism of the actions of leukotrienes indicates that the compounds and pharmaceutical compositions

thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) cardiovascular disorders such as angina, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as Interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small- and large-airway diseases, and 15) cholecystitis.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion; dysmenorrhea; ischemia; noxious agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by

hepatoxic agents such as CCl_4 and D- galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also exhibit cytoprotective action.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions, and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay and are described in EP 140,684.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or

anti-inflammatory use and generally, uses other than cytoprotection, lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory, or anti-allergic use is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

The exact amount of a compound of the Formula I to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastrointestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of the use of a compound of the Formula I in avoiding future damage would be co-administration of a compound of the Formula I with an NSAID that might otherwise cause such damage (for example, indomethacin). For such use, the compound of Formula I is administered from 30 minutes prior up to 30 minutes after administration of the NSAID. Preferably it is administered prior to or simultaneously with the NSAID, (for example, in a combination dosage form).

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic

ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosures of which are hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 2.5 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 2.5 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1 mL	

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula I	24 mg
Lecithin, NF Liquid Concentrate	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

Combinations with Other Drugs

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

(1) propionic acid derivatives;
(2) acetic acid derivatives;
(3) fenamic acid derivatives;
(4) oxicams; and
(5) biphenylcarboxylic acid derivatives,

or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, prano-profen, suprofen, tiaprofenic acid, and tioxaprofen. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

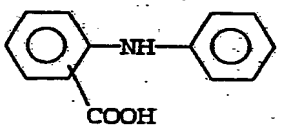
The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac. Structually related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically

acceptable salt group, e.g. $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

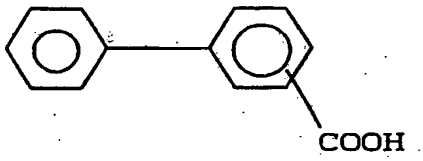
Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

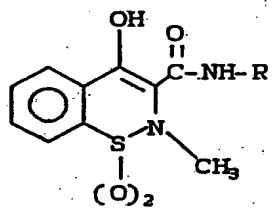
Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The oxicams which can be used in the present invention comprise: isoxicam, piroxicam, sudoxicam and tenoxican. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used: amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate,

benzydanine, beprozin, broperamole, bufezolac, cinmetacin, ciproquazone, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclorac, fendosal, fenflumizole, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furcloprofen, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim, isoprofen, isoxicam, lefetamine HCl, leflunomide, lofemizole, lonazolac calcium, lotifazole, loxoprofen, lysin clonixinate, meclofenamate sodium, meseclazone, nabumetone, nictindole, nimesulide, orpanoxin, oxametacin, oxapadol, perisoxal citrate, pimeprofen, pimetacin, piproxen, pirazolac, pirfenidone, proglumetacin maleate, proquazone, pyridoxiprofen, sudoxicam, talmetacin, talniflumate, tenoxicam, thiazolinobutazone, thielavin B, tiaramide HCl, tiflamizole, timegadine, tolpadol, tryptamid, and ufenamate.

The following NSAIDs, designated by company code number (see e.g., Pharmaprojects), may also be used:
480156S, AA861, AD1590, AFP802, AFP860, AI77B, AP504, AU8001, BPPC, BW540C, CHINOIN 127, CN100, EB382, EL508, F1044, GV3658, ITF182, KCNTEI6090, KME4, LA2851, MR714, MR897, MY309, ON03144, PR823, PV102, PV108, R830, RS2131, SCR152, SH440, SIR133, SPAS510, SQ27239, ST281, SY6001, TA60, TAI-901 (4-benzoyl-1-indancarboxylic acid), TVX2706, U60257, UR2301, and WY41770.

Finally, NSAIDs which may also be used include the salicylates, specifically acetyl salicylic acid and the phenylbutazones, and pharmaceutically acceptable salts thereof.

In addition to indomethacin, other preferred NSAIDs are acetyl salicylic acid, diclofenac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolmetin.

Pharmaceutical compositions comprising the Formula I compounds may also contain inhibitors of the biosynthesis of the leukotrienes such as are disclosed in EP 138,481 (April 24,1985), EP 115,394 (August 8, 1984), EP 136,893 (April 10, 1985), and EP 140,709 (May 8, 1985), which are hereby incorporated herein by reference.

The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP 106,565 (April 25, 1984) and EP 104,885 (April 4, 1984) which are hereby incorporated herein by reference and others known in the art such as those disclosed in EP Application Nos. 56,172 (July 21, 1982) and 61,800 (June 10, 1982); and in U.K. Patent Specification No. 2,058,785 (April 15, 1981), which are hereby incorporated herein by reference.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, prostaglandin antagonists such as those disclosed in EP 11,067 (May 28, 1980) or thromboxane antagonists such as those disclosed in U.S. Pat. 4,237,160. They may also contain histidine

decarboxylase inhibitors such as α-fluoromethyl-histidine, described in U.S. Pat. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1- or H_2-receptor antagonist, such as for instance acetamazole, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981), benadryl, cimetidine, famotidine, framamine, histadyl, phenergan, ranitidine, terfenadine and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; and 4,394,508. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Compounds of Formula I may also be usefully combined with most cell stabilizing agents, such as 1,3-bis(2-carboxy-chromon-5-yloxy)-2-hydroxypropane and related compounds described in British Patent Specifications 1,144,905 and 1,144,906. Another useful pharmaceutical composition comprises the Formula I compounds in combination with serotonin antagonists such as methysergide, the serotonin antagonists described in Nature, 316, 126-131 (1985), and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

Other advantageous pharmaceutical compositions comprise the Formula I compounds in combination with anti-cholinergics such as ipratropium bromide, bronchodilators such as the beta agonist salbutamol, metaproterenol, terbutaline, fenoterol and the like, and the anti-asthmatic drugs theophylline, choline theophyllinate and enprofylline, the calcium antagonists nifedipine,

diltiazem, nitrendipine, verapamil, nimodipine, felodipine, etc. and the corticosteroids, hydrocortisone, methylprednisolone, betamethasone, dexamethasone, beclomethasone, and the like.

Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods.

Scheme 1

2-Benzoyloxymethylbenzothiazole of general structure IV is prepared by the condensation of α-bromoketone II (readily available by bromination of the corresponding ketone) and 2-benzoyloxythioacetamide III (Olin and Johnson, Rec. Trav. Chim., 1931, 50, 72) in refluxing ethanol. Hydrolysis of the ester of IV followed by treatment of the resulting alcohol with thionyl chloride gives the corresponding chloride which is then converted to the corresponding phosphonium salt V by refluxing the former with triphenylphosphine in acetonitrile. The chlorides or bromides IVa can also be prepared by reaction of NCS or NBS with the corresponding 2-methylthiazoles.

Scheme 2

Dialdehyde VI is half reduced with sodium borohydride. The resulting alcohol is protected as its tetrahydropyranyl ether VII which is then treated with vinyl magnesium bromide or allyl magnesium bromide to give the alcohol VIII. Coupling of VIII with bromide IX in the presence of palladium acetate gives the keto ester X. Reduction of the ketone with the complex XI (J. Am. Chem. Soc., 104, 5551-5553,

1987), followed by alkylation of the ester with an alkyl Grignard or an alkyl cerium reagent, gives the diol XII. (To obtain compound XII with one R^2 = H, one equivalent of Grignard reagent is used and the initially formed ketone is reduced to the corresponding benzyl alcohol.)

The chiral alcohol of the diol XII is first protected as the t-butyl dimethyl silyl ether. The other benzylic alcohol is protected as a tetrahydropyranyl ether which is then treated with tetrabutyl ammonium fluoride to give the alcohol XIII. Mesylation of XIII, followed by displacement of the resulting mesylate with the appropriate substituted thiol XIV, gives the thiol ether XV. Removal of the THP protecting groups from XV with PPTS in methanol followed by oxidation of the primary benzylic alcohol with manganese dioxide in ethyl acetate gives aldehyde XVI. Coupling of V and XVI gives the olefin-linked benzothiazole benzyl alcohol XVII (I).

Scheme 3

Reaction of XVII with trimethylsulfonium iodide and a base such as DMSO anion gives the cyclopropyl linked compound XVIII (I). Reduction of the olefin of XVII with borane gives the saturated compound XIX (I).

Starting from benzaldehyde XX and following the same sequence as described above for aldehyde VII, the compound XXI can be prepared which may be coupled with the halide III to give the ether linked benzothiazole benzylalcohol XXII (I).

It will be obvious to one skilled in the art that compounds XVII, XVIII, XIX, or XXII having the

opposite stereochemistry at the sulfur-bearing benzylic carbon can be obtained by using the opposite stereoisomer of the reduction catalyst XI to reduce X to XII or by inversion of the stereocenter in XIII by a Mitsunobu reaction (Synthesis, 1-28, 1981).

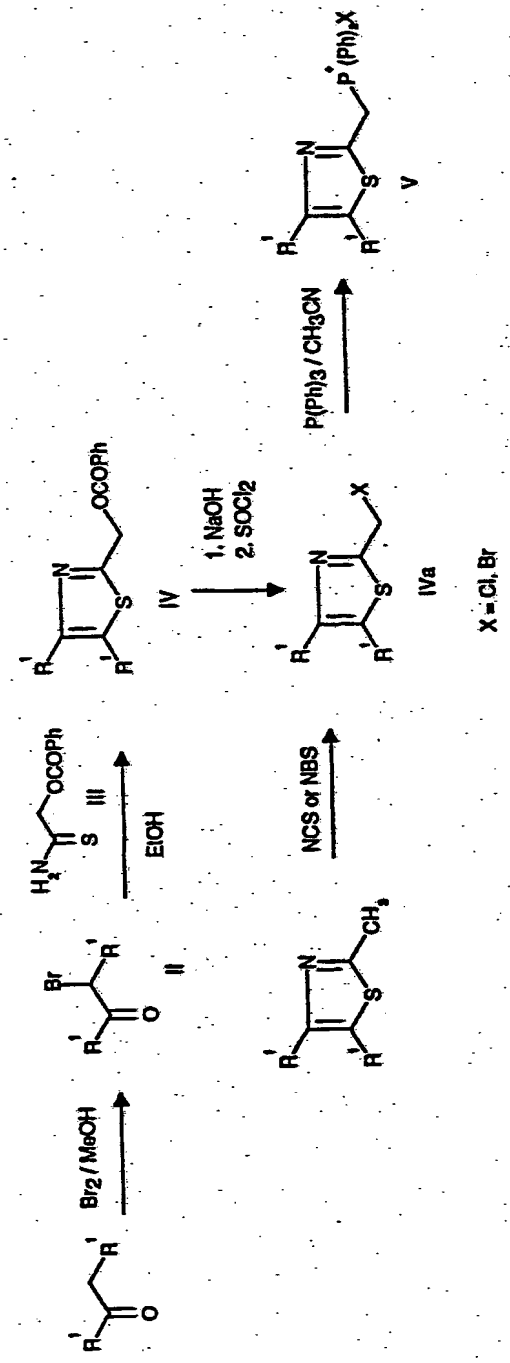
Scheme 4

Reduction of keto aldehyde XXIII, followed by protection of the corresponding alcohol as the tetrahydropyranyl ether, gives XXIV. The enolate of ketone XXIV, obtained by treatment of XXIV with a base such as KH or NaH is reacted with dimethyl-carbonate to yield the ketoester XXV. Alkylation of XXV with iodide XXVI followed by decarboxylation of the resulting adduct using conditions such as heating with HCl in acetic acid affords the ketone XXVII. In the case where the THP ether is cleaved, the alcohol is reprotected as the THP ether. Following the procedure described in Scheme 2, ketone XXVII is transformed to XXVIII, a structure representative of I.

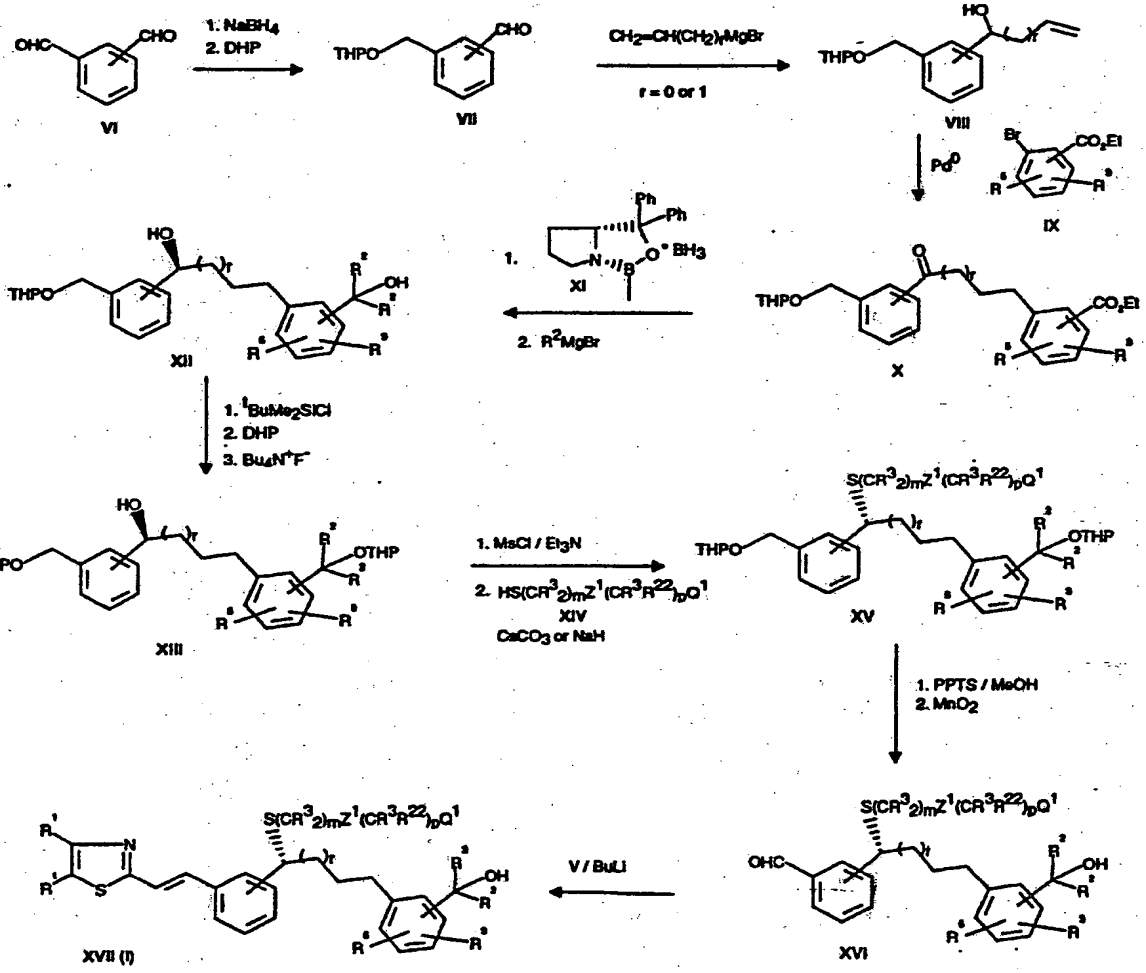
Scheme 5

Iodoacid XXIX is treated with 2 equivalents of a base such as n-butyllithiam in a suitable solvent such as THF at -100°C, then at -78°C to afford XXX, which is reacted with aldehyde VII to yield the hydroxyacid XXXI. The hydroxyacid XXXI is then esterified using conditions such as CH_2N_2 or MeI/Cs_2CO_3 and an organometallic reagent is then added to give the diol XXXII. Following the same procedure as described in Scheme 2, the benzylic alcohol is transformed to XXXIII, which is a structure representative of I.

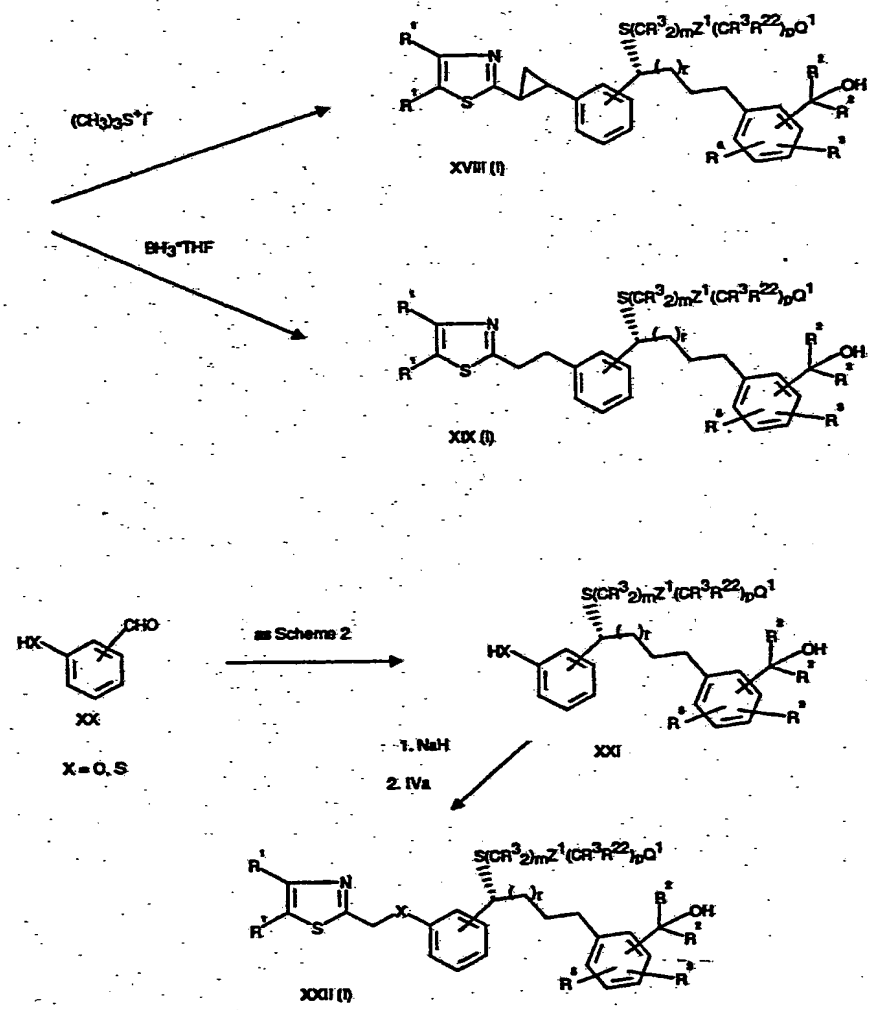
SCHEME 1


P(Ph)2X
V
P(Ph)3 / CH3CN
OCOPh
1. NaOH
2. SOCl2
IV
X
IVa
X = Cl, Br
NCS or NBS
EtOH
III
II
Br2 / MeOH

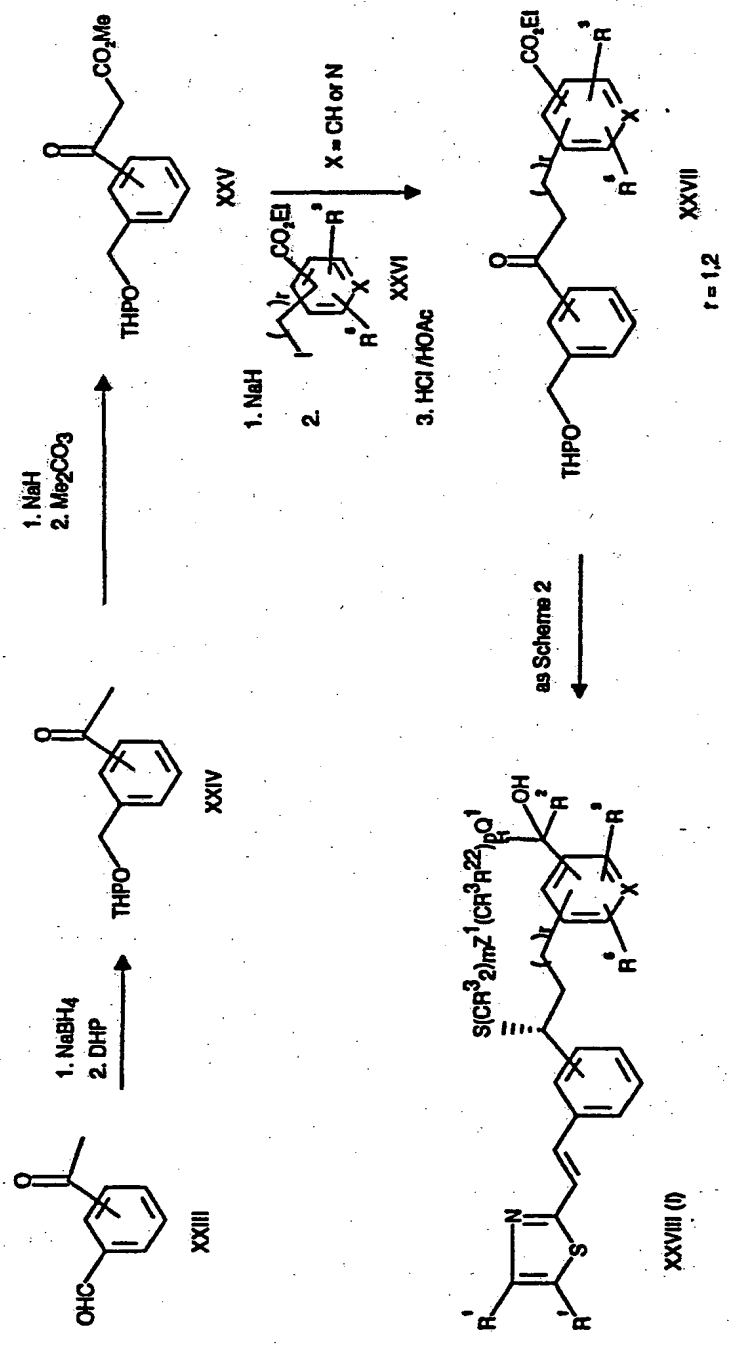
SCHEME 2


1. NaBH4
2. DHP
CH2=CH(CH2)rMgBr
r = 0 or 1
Pd0
1.
2. R2MgBr
1. tBuMe2SiCl
2. DHP
3. Bu4N+F-
1. MsCl / Et3N
2. HS(CR32)mZ1(CR3R22)pQ1
XIV
CsCO3 or NaH
1. PPTS / MeOH
2. MnO2
V / BuLi
VI
VII
VIII
IX
X
XI
XII
XIII
XV
XVI
XVII (I)

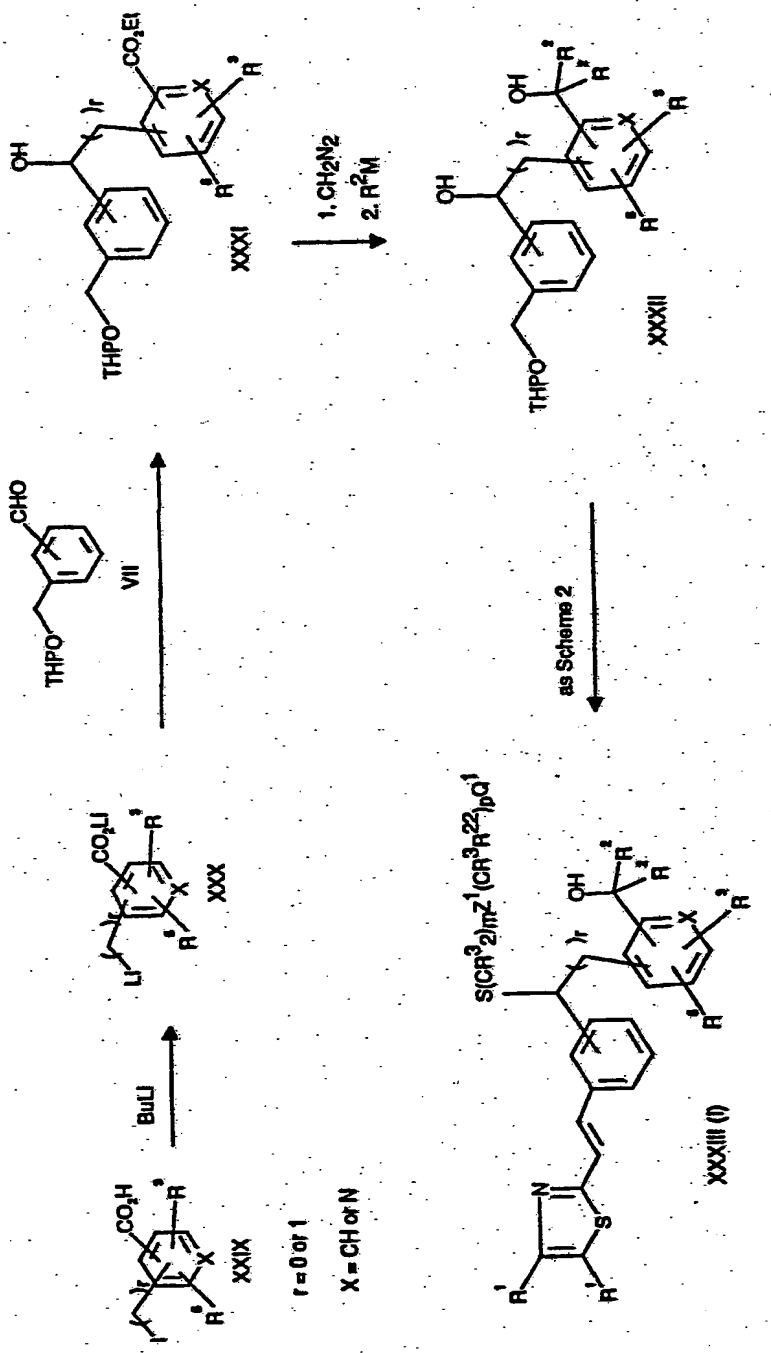
SCHEME 3


XVII
(CH3)3S+I-
BH3•THF
XVIII (I)
XIX (I)
as Scheme 2
XX
X = O, S
XXI
1. NaH
2. IVa
XXII (I)

SCHEME 4

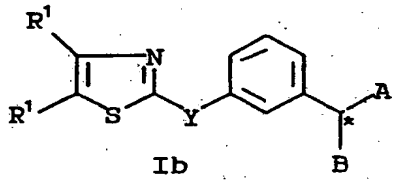

CO2Me
THPO
XXV
X = CH or N
1. NaH
2.
3. HCl/HOAc
XXVI
CO2Et
XXVII
r = 1,2
1. NaH
2. Me2CO3
as Scheme 2
XXIV
1. NaBH4
2. DHP
XXIII
OHC
XXVIII (I)

SCHEME 5


CO2Et
OH
THPO
XXXI
1. CH2N2
2. R2M
XXXII
CHO
VII
as Scheme 2
CO2Li
Li
XXX
BuLi
CO2H
XXIX
r = 0 or 1
X = CH or N
S(CR3 2)mZ1(CR3R22)pQ1
XXXIII (I)

Representative Compounds

Table I illustrates compounds of formula Ib, which are representative of the present invention.



Ib

TABLE I

EX. No.	*	R^1	R^1	Y	A	B
1	R	H	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
2	R	4-i-Pr	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
3	R	4-c-Bu	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
4	R	4-c-Pen	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
5	R	4-c-Hex	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
6	R	4-i-Pr	5-Me	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
7	R	4-i-Pr	5-Cl	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
8	R	$-(CH_2)_4-$		CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
9	R	4-Ph	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
10	R	4-(4-F-Ph)	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
11	R	4-(4-Cl-Ph)	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
12	R	4-(4-OMe-Ph)	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$-
13	R	4-c-Pr	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
14	R	4-t-Bu	H	CH=CH	$(CH_2)_2$(1,2-phe)C$(Me)_2$OH	$SCH_2C(CH_2)_2CH_2CO_2H$
15	R	4-c-Pr	H	CH_2CH_2	$(CH_2)_2$(4-Cl-1,2-phe)C$(Me)_2$OH	$OCH_2C(CH_3)_2CH_2CO_2H$
16	S	4-t-Bu	5-c-Bu	CH_2O	$(CH_2)_2$(4-Cl-1,2-phe)C$(Me)_2$OH	$OCH_2CH(CH_3)CH_2T_z$
17	R	4-c-Pen	5-F	CH(-CH_2-)CH	$(CH_2)_2$(4-F-1,2-phe)C$(Me)_2$OH	$SCH_2CH(C_2H_5)CH_2CONMe_2$
18	S	4-Et	5-Me	$CH(CH_3)CH(CH_3)$	CH_2(4-F-1,2-phe)CMePhOH	$SCH_2CH_2CO_2H$
19	RS	4-CH_2Ph	5-CF_3	CH(-$C(CH_3)_2$-)CH	$(CH_2)_2$(3-Cl-1,2-phe)CHMeOH	$SCH_2CH_2CONHS(O)_2Ph$

TABLE I (cont'd)

Ex. No.	*	R^1	R^1	Y	A	B
20	R	4-c-Pr	H	CH_2S	$(CH_2)_2$(5-F-1,2-phe)$CMeCF_3OH$	$SCH_2CH_2CONHS(O)_2CH_3$
21	R	4-$PhSCH_2$	5-Et	$CH(CH_3)CH_2$	(6-CF_3-1,2-phe)$CHCF_3OH$	$SCH_2CH_2CONHS(O)_2CF_3$
22	S	-$(CH_2)_3$-		CH=CH	$(CH_2)_2$(4-CF_3-1,2-phe)$C(CF_3)_2OH$	$SCH_2C(CH_2)_2CH_2CONHS(O)_2Ph$
23	R	4-(2-Fu)	5-F	CH_2CH_2	$(CH_2)_2$(4-F-1,3-phe)CMeEtOH	$CH_2CH_2C(CH_3)_2CO_2H$
24	R	4-(2-Py)	H	CH_2CH_2	$(CH_2)_2$(4-F-1,4-phe)$C(CH_2)_2OH$	$SCH_2CH(C_2H_5)Tz$
25	R	4-(2-Th)	H	CH=CH	$(CH_2)_2$(4-F-1,2-phe)$C(CH_2)_3OH$	$SCH_2C(CH_2)_2NHS(O)_2CF_3$
26	S	4-CN	H	CH=CH	$(CH_2)_2$(4-F-1,2-phe)$C(CH_2)_4OH$	$SCH_2C(CH_2)_3CH_2CO_2H$
27	R	4-CF_3	H	CH_2CH_2	$(CH_2)_2$(4-F-1,2-phe)$C(CH_2)_5OH$	$SCH_2C(CH_2)_4CH_2CO_2H$
28	S	4-c-Bu	5-OMe	CH_2O	$(CH_2)_2$(2,5-fur)$C(Me)_2OH$	$SCH_2C(CH_2)_5CH_2CO_2H$
29	RS	4-c-Pen	5-Bu	$CH(-CH_2-)CH$	$(CH_2)_2$(1,2-phe)$C(Me)_2OH$	$SCH_2C(CH_3)_2CH_2CO_2H$
30	R	4-c-Hex	H	$CH(CH_3)CH(CH_3)$	$(CH_2)_2$(2,5-thio)$C(Me)_2OH$	$SCH_2CH(CH_3)CH_2Tz$
31	R	-$(CH_2)_4$-		$CH(-C(CH_3)_2-)CH$	$(CH_2)_2$(2,6-pye)$C(Me)_2OH$	$SCH_2CH(C_2H_5)CH_2CONMe_2$
32	R	4-c-Bu	H	CH_2S	$(CH_2)_2$(2,4-pye)$C(Me)_2OH$	$SCH_2CH_2CO_2H$

Assays for Determining Biological Activity

The leukotriene antagonist properties of the compounds of the present invention are evaluated using the following assays.

Three assays are described in T.R. Jones et al., Can. J. Physiol. Pharmacol., 1989, 67, 17-28. These are:

1) LTD_4 Receptor Binding Assays in Guinea Pig Lung Membranes,
2) Guinea Pig Trachea, and
3) In Vivo Assays in Anesthetized Guinea Pigs.

Asthmatic Rat Assay

Rats are obtained from an inbred line of asthmatic rats. Both female (190-250 g) and male (260-400 g) rats are used.

Egg albumin (EA), grade V, crystallized and lyophilized, is obtained from Sigma Chemical Co., St. Louis. Aluminum hydroxide is obtained from the Regis Chemical Company, Chicago. Methysergide bimaleate is supplied by Sandoz Ltd., Basel.

The challenge and subsequent respiratory recordings are carried out in a clear plastic box with internal dimensions 10x6x4 inches. The top of the box is removable; in use, it is held firmly in place by four clamps and an airtight seal is maintained by a soft rubber gasket. Through the center of each end of the chamber a DeVilbiss nebulizer (No. 40) is inserted via an airtight seal and each end of the box also has an outlet. A

Fleisch No. 0000 pneumotachograph is inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which is then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the outlets are open and the pneumotachograph is isolated from the chamber. The outlets are closed and the pneumotachograph and the chamber are connected during the recording of the respiratory patterns. For challenge, 2 mL of a 3% solution of antigen in saline is placed into each nebulizer and the aerosol is generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

Rats are sensitized by injecting (subcutaneously) 1 mL of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. They are used between days 12 and 24 postsensitization. In order to eliminate the serotonin component of the response, rats are pretreated intravenously 5 minutes prior to aerosol challenge with 3.0 mg/kg of methysergide. Rats are then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles are recorded for a further 30 minutes. The duration of continuous dyspnea is measured from the respiratory recordings.

Compounds are generally administered either orally 1-4 hours prior to challenge or intravenously 2 minutes prior to challenge. They are either dissolved in saline or 1% methocel or suspended in 1% methocel. The volume injected is 1 mL/kg (intravenously) or 10 mL/kg (orally). Prior to oral treatment rats are starved overnight. Their activity

is determined in terms of their ability to decrease the duration of symptoms of dyspnea in comparison with a group of vehicle-treated controls. Usually, a compound is evaluated at a series of doses and an ED_{50} is determined. This is defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

Pulmonary Mechanics in Trained Conscious Squirrel Monkeys

The test procedure involves placing trained squirrel monkeys in chairs in aerosol exposure chambers. For control purposes, pulmonary mechanics measurements of respiratory parameters are recorded for a period of about 30 minutes to establish each monkey's normal control values for that day. For oral administration, compounds are dissolved or suspended in a 1% methocel solution (methylcellulose, 65HG, 400 cps) and given in a volume of 1 mL/kg body weight. For aerosol administration of compounds, a DeVilbiss ultrasonic nebulizer is utilized. Pretreatment periods vary from 5 minutes to 4 hours before the monkeys are challenged with aerosol doses of either leukotriene D_4 (LTD_4) or Ascaris suum antigen.

Following challenge, each minute of data is calculated by computer as a percent change from control values for each respiratory parameter including airway resistance (R_L) and dynamic compliance (C_{dyn}). The results for each test compound are subsequently obtained for a minimum period of 60 minutes post challenge which are then

compared to previously obtained historical baseline control values for that monkey. In addition, the overall values for 60 minutes post-challenge for each monkey (historical baseline values and test values) are averaged separately and are used to calculate the overall percent inhibition of LTD_4 or Ascaris antigen response by the test compound. For statistical analysis, paired t-test is used. (References: McFarlane, C.S. et al., Prostaglandins, 28, 173-182 (1984) and McFarlane, C.S. et al., Agents Actions, 22, 63-68 (1987).)

Prevention of Induced Bronchoconstriction in Allergic Sheep

A. Rationale:

Certain allergic sheep with known sensitivity to a specific antigen (Ascaris suum) respond to inhalation challenge with acute and late bronchial responses. The time course of both the acute and the late bronchial responses approximates the time course observed in asthmatics and the pharmacological modification of both responses is similar to that found in man. The effects of antigen in these sheep are largely observed in the large airways and are conveniently monitored as changes in lung resistance or specific lung resistance.

B. Methods:

Animal Preparation: Adult sheep with a mean weight of 35 kg (range, 18 to 50 kg) are used. All animals used meet two criteria: a) they have a natural cutaneous reaction to 1:1,000 or 1:10,000 dilutions of Ascaris suum extract (Greer Diagnostics, Lenois, NC) and b) they have previously responded to inhalation challenge with Ascaris suum with both an acute bronchoconstriction and a late bronchial obstruction (W.M. Abraham et al., Am. Rev. Resp. Dis., 128, 839-44 (1983)).

Measurement of Airway Mechanics: The unsedated sheep are restrained in a cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril using a flexible fiberoptic bronchoscope as a guide. Pleural pressure is estimated with the esophageal balloon catheter (filled with one ml of air), which is positioned such that inspiration produces a negative pressure deflection with clearly discernible cardiogenic oscillations. Lateral pressure in the trachea is measured with a sidehole catheter (inner dimension, 2.5 mm) advanced through and positioned distal to the tip of the nasotracheal tube. Transpulmonary pressure, the difference between tracheal pressure and pleural pressure, is measured with a differential

pressure transducer (DP45; Validyne Corp., Northridge, CA). For the measurement of pulmonary resistance (R_L), the maximal end of the nasotrachel tube is connected to a pneumotachograph (Fleisch, Dyna Sciences, Blue Bell, PA). The signals of flow and transpulmonary pressure are recorded on an oscilloscope (Model DR-12; Electronics for Medicine, White Plains, NY) which is linked to a PDP-11 Digital computer (Digital Equipment Corp., Maynard, MA) for on-line calculation of R_L from transpulmonary pressure, respiratory volume obtained by integration and flow. Analysis of 10-15 breaths is used for the determination of R_L. Thoracic gas volume (V_{tg}) is measured in a body plethysmograph, to obtain specific pulmonary resistance ($SR_L = R_L \cdot V_{tg}$).

Aerosol Delivery Systems: Aerosols of Ascaris suum extract (1:20) are generated using a disposable medicalnebulizer (Raindrop®, Puritan Bennett), which produces an aerosol with a mass median aerodynamic diameter of 6.2 μM (geometric standard deviation, 2.1) as determined by an electric size analyzer (Model 3030; Thermal Systems, St. Paul, MN). The output from the nebulizer is directed into a plastic t-piece, one end of which is attached to the nasotracheal tube, the other end of which is conected to the inspiratory part of a Harvard respirator. The aerosol is delivered at a tidal volume of 500 mL of a rate of 20 per minute. Thus, each sheep receives an equivalent dose of antigen in both placebo and drug trials.

Experimental Protocol: Prior to antigen challenge baseline measurements of SR_L are obtained, infusion of the test compound is started 1 hr prior to challenge, the measurement of SR_L repeated and then the sheep undergoes inhalation challenge with Ascaris suum antigen. Measurements of SR_L are obtained immediately after antigen challenge and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, and 8 hrs after antigen challange. Placebo and drug tests are separated by at least 14 days. In a further study, sheep are given a bolus dose of the test compound followed by an infusion of the test compound for 0.5-1 hr prior to Ascaris challenge and for 8 hrs after Ascaris as described above.

Statistical Analysis: A Kruskal-Wallis one way ANOVA test is used to compare the acute immediate responses to antigen and the peak late response in the controls and the drug treated animals.

The invention is further defined by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) all final products were essentially pure by TLC and had satisfactory nuclear magnetic resonance (NMR) spectra and microanalytical data;

(vi) yields are given for illustration only and, for crystalline end-products, refer to the weight of recrystallized solid;

(vii) when given, NMR data are in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 250 MHz or 300 MHz using the indicated solvent; conventional abbreviations for signal shape are used (for example, s. singlet; d. doublet; m. multiplet; br. broad); "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)), hr (hour(s)).

EXAMPLE 1

Sodium 1-(((1(R)-((3-(2-(2-thiazolyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)-methyl)cyclopropaneacetate

Step 1: 2-Benzoyloxymethylthiazole

To a solution of 1,2-dichloroethyl ethyl ether (1.75 g, 12.3 mmol) in benzene was added 2-benzoyloxythioacetamide (1.2 g, 6.15 mmol) (Olin et al., Rec. trav. chim., 50, 72 (1931)). The mixture was refluxed for 4 hr. Aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 20% EtOAc in hexane) gave 700 mg (52%) of the title compound.

Step 2: 2-Chloromethylthiazole

To a solution of the product of Step 1 (700 mg, 3.2 mmol) in MeOH (4 mL) and THF (4 mL) was added NaOH (2N, 7 mL). The mixture was stirred at 25°C for 2 hr. Aqueous NH_4Cl was added and the mixture was

extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 50% EtOAc in hexane) gave 316 mg (86%) of the corresponding alcohol. The alcohol was then treated with $SOCl_2$ (402 mg, 3.38 mmol) and the mixture was refluxed for 1 hr. Aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated to give 350 mg (96 %) of the title compound as an oil which was used in the next step without further purification.

Step 3: 2-Thiazolylmethyl triphenylphosphonium chloride

To a solution of 2-chloromethylthiazole (350 mg, 2.6 mmol) in CH_3CN (5 mL) was added $P(Ph)_3$ (686 mg, 5.2 mmol). The mixture was refluxed for 20 hr and was then concentrated to 1/3 of its original volume. Et_2O (8 mL) was added. The mixture was stirred vigorously and the crystalline salt was filtered and washed with more Et_2O to give 862 mg (84%) of the title compound.

Step 4: 1,1-Cyclopropanedimethanol cyclic sulfite

To a solution of BH_3:THF complex (1M in THF, 262 mL) was added diethyl 1,1-cyclopropanedicarboxylate (25 g, 134 mmol) at 25°C under N_2. The solution was heated at reflux for 6 hr, cooled to r.t., and MeOH (300 mL) was cautiously added. The solution was stirred for 1 hr and then concentrated to an oil. The crude diol was dissolved in CH_2Cl_2

(234 mL) and $SOCl_2$ (15.9 g, 134 mmol) was added dropwise over a period of 15 min at 25°C. After stirring for another 15 min, the mixture was washed with aqueous $NaHCO_3$. The organic extract was dried over Na_2SO_4, filtered and concentrated to give quantitatively the title compound as a white solid.

Step 5: 1-(Hyroxymethyl)cyclopropaneacetonitrile

To a solution of the cyclic sulfite product of Step 4 (14.7 g, 99 mmol) in DMF (83 mL) was added NaCN (9.74 g, 199 mmol). The mixture was heated to 90°C for 20 hr. Upon cooling, EtOAc (400 mL) was added and the solution was washed with saturated $NaHCO_3$ solution (55 mL), H_2O (4x 55 mL), saturated NaCl solution and dried over Na_2SO_4. The solution was concentrated to give 7.1 g (65%) of the title compound.

Step 6: 1-(Acetythiomethyl)cyclopropaneacetonitrile

To a solution of the alcohol of Step 5 (42 g, 378 mmol) in dry CH_2Cl_2 (450 mL) at -30°C was added Et_3N (103.7 mL, 741 mmol) followed by CH_3SO_2Cl (43.3 mL, 562 mmol) dropwise. The mixture was warmed to 25°C, washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give the corresponding mesylate. The mesylate was then dissolved in DMF (450 mL) and cooled to 0°C. Potassium thioacetate (55.4 g, 485 mmol) was added, and the mixture was stirred at 25°C for 18 hr. EtOAc (1.5 L) was added, the solution was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give 45 g (70%) of the title compound.

Step 7: Methyl 1-(thiomethyl)cyclopropaneacetate

To a solution of the nitrile of Step 6 (45 g, 266 mmol) in MeOH (1.36 L) was added H_2O (84 mL) and conc. H_2SO_4 (168 mL). The mixture was heated to reflux for 20 hr, cooled to 25°C, H_2O (1 L) was added and the product was extracted with CH_2Cl_2 (2x 1.5 L). The organic extract was washed with H_2O and dried over Na_2SO_4. Concentration of the organic solution gave 36 g (93%) of the title compound.

Step 8: 3-(2-Tetrahydropyranyl)oxymethyl benzaldehyde

Isophthalaldehyde (150 g, 1.1 mole) was dissolved in THF (1 L) and EtOH (1 L) at 0°C. $NaBH_4$ (11.0 g, 291 mmol) was added portionwise and the mixture stirred 1 hour at 0°C. Addition of 25% aq. NH_4OAc and extraction with EtOAc (2x) followed by purification by flash chromatography (20% → 40% EtOAc in hexanes) yielded 60 g of m-hydroxymethyl benzaldehyde.

This alcohol (0.44 mole) was dissolved in CH_2Cl_2 (500 ml), DHP (50 g, 0.59 mole) and PTSA (1 g, 5 mmol) were added and the mixture was stirred overnight at r.t. After concentration in vacuo, the residue was purified by flash chromatography (5% → 15% EtOAc in toluene) to give 85 g of the title compound.

Step 9: 1-((3-(2-Tetrahydropyranyl)oxymethyl)-phenyl)pro-2-ene-1-ol

To the aldehyde of Step 8 (85 g, 386 mmol) in toluene (1 L) at 0°C was slowly added vinyl magnesium bromide in Et_2O (450 ml, 1 M, 450 mmol)

over a 30 minute period. After stirring for 1 hour, the reaction mixture was quenched with 25% aq. NH_4OAc and extracted with EtOAc (3x). Evaporation and purification by flash chromatography (15% → 25% EtOAc in toluene) yielded 82 g (86%) of the title compound.

Step 10: Ethyl 2-((3-(3-(2-tetrahydropyranyl) oxymethyl)phenyl)-3-oxo))propylbenzoate

The allylic alcohol of Step 9 (24.8 g, 100 mmol) and ethyl o-bromobenzoate (25.2 g, 110 mmol) were dissolved in DMF (200 mL). LiCl (4.2 g, 100 mmol), $LiOAc \cdot 2H_2O$ (25.5 g, 250 mmol) and $n\text{-}Bu_4N^+Cl^-$ (55 g, 200 mmol) were added and the resulting mixture was degassed three times. $Pd(OAc)_2$ (1 g) was then added and the mixture was degassed three more times before heating it at 100°C with stirring for 1 hour. After cooling to r.t., the reaction mixture was poured onto H_2O (600 mL), 10% aq. $NaHCO_3$ (200 mL) and Et_2O. The crude product was extracted with Et_2O (2x), washed with H_2O and brine, and dried over Na_2SO_4 before concentrating in vacuo. Purification on a short silica gel column (20% EtOAc in hexanes) gave 34 g (86%) of the title compound.

^1H NMR (CD_3COCD_3): δ 8.02 (1H, bs), 7.92 (1H, d), 7.88 (1H, d), 7.65 (1H, d), 7.50 (3H, m), 7.32 (1H, bt), 4.8 (1H, d), 4.70 (1H, bs), 4.54 (1H, d), 4.3 (2H, q), 3.82 (1H, m), 3.50 (1H, m), 3.35 (4H, m), 1.9-1.45 (6H, m), 1.32 (3H, t).

Step 11: 1(S)-Ethyl 2-(3-hydroxy-3-((3-(2-tetrahydropyranyl)oxymethyl)phenyl)propyl benzoate

The keto-ester of Step 10 (24.8 g, 62.5 mmol) was dissolved in THF (230 mL) and cooled to -45°C. A THF (15 mL) solution of tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]-oxazoborole-borene adduct (J. Org. Chem. 56, 751 (1991), 4.55 g, 15.6 mmol) was added dropwise and the resulting mixture was stirred 20 minutes at -45°C. To this solution, 1.0M borane in THF (62.5 mL, 62.5 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred 1 hour at -45°C followed by another 2 hours with slow warming to -20°C. After cooling the solution to -40°C, it was poured onto 25% aq. NH_4OAc (425 mL) and 1.0 M diethanolamine (40 mL) at 0°C and stirred vigorously for 20 minutes. The title compound was extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography (25% to 50% EtOAc in hexanes) to yield 22.6 g (91%) of the product as an oil.

$[\alpha]_D^{25} = -32.6°$ (C = 3, $CHCl_3$)

Step 12: 1(S)-((3-(2-Tetrahydropyranyl)oxymethyl)-phenyl)-3-((2-(1-hydroxy-1-methyl)ethyl)-phenyl)propan-1-ol

Anhydrous $CeCl_3$ (17.25 g, 70 mmol) was refluxed for 2.5 hours in THF (200 mL) using a Dean-Stark trap filled with molecular sieves to remove H_2O. The ivory suspension was cooled to -5°C and MeMgCl (114 mL, 3 Mn in THF, 340 mmol) was added

dropwise while keeping the internal temperature between -10°C and 0°C. The grey suspension was stirred 2 hours before slowly adding to it the hydroxy-ester of Step 11 (27.1 g, 68 mmol) as a THF solution (200 mL) via a cannula. The resulting mixture was stirred 1.5 hours at or below 0°C, and then slowly poured onto ice cold 1M HOAc (1 L) and EtOAc (500 ml) and stirred for 30 minutes. After adjusting the pH to 6-7, the crude compound was extracted with EtOAc (2x) and the combined organic phases were washed with saturated $NaHCO_3$ aq. followed with brine. Purification on a short silica gel column (30% to 50% EtOAc in hexanes) yielded 24.5 g (95%) of the title compound.

Step 13: Methyl 1-(((1(R)-((3-(2-tetrahydropyranyl)-oxymethyl)phenyl))-3-(2-(1-hydroxy-1-methyl)ethyl)phenyl)thio)methyl)cyclo-propaneacetate

The diol of Step 12 (17.9 g, 46.6 mmol) was dissolved in CH_3CN (40 mL) and DMF (10 mL) and cooled to -42°C under nitrogen. Diisopropylethyl-amine (8.5 mL, 48.9 mmol) was added followed by methanesulphonyl chloride (3.6 mL, 46.6 mmol) dropwise. The solution was stirred 1.5 hours with a mechanical stirring while maintaining the temperature between -42° and -35°C; then it was cooled to -45°C. The thiol of Step 7 (7.84 g, 48.9 mmol) was added followed by dropwise addition of DMF (15 mL). Potassium tert -butoxide in THF (56 mL, 1.75 M, 97.9 mmol) was added to the reaction mixture over 20

minutes using a syringe pump. Stirring was continued for 5 hours with slow warming from -35°C to -22°C, giving a very thick translucid gel. The reaction was quenched with saturated aq. NH_4Cl (250 mL) and EtOAc (300 mL). The product was extracted with EtOAc, washed with H_2O and brine, and dried over $MgSO_4$. Purification by flash chromatography (20% to 30% EtOAc in hexanes) gave 16.8 g (68%) of the title compound.

Step 14: Methyl 1-(((1(R)-(3-(hydroxymethyl)phenyl)-3-(2-(1-hydroxy-1-methyl)ethyl)phenyl)-thio)methyl)cyclopropaneacetate

To the hydroxy ester from Step 13 (9.02 g, 17.1 mol) in anhydrous MeOH (60 mL) under nitrogen was added pyridine (50 µL) followed by PPTS (1.1 g, 4.3 mmol). The reaction mixture was stirred 3.5 hours at 55°C, then at r.t. overnight before concentrating in vacuo. The residue was diluted with EtOAc (500 mL) and washed with H_2O, saturated aq. $NaHCO_3$, NaH_2PO_4 buffer (pH = 4.5) and with brine. After drying over $MgSO_4$ and evaporation of the solvents, the residue was purified by flash chromatography (40% to 60% EtOAc in hexanes) giving 6.85 g (91%) of the title compound.
^1H NMR (CD_3COCD_3): δ 7.41 (2H, m), 7.27 (3H, m), 7.09 (3H, m), 4.63 (2H, d), 4.19 (1H, t), 3.95 (1H, t), 3.88 (1H, s), 3.57 (3H, s), 3.1 (1H, ddd), 2.8 (1H, ddd), 2.5 (2H, s), 2.4 (2H, d), 2.17 (2H, m), 1.52 (6H, s), 0.52-0.35 (4H, m).

Step 15: Methyl 1-((((1R)-3-(formyl)phenyl)-3-(2-(1-hydroxy-1-methyl)ethyl)phenyl)thio)-methyl)cyclopropaneacetate

To the dihydroxy ester from Step 14 (6.8 g, 15.4 mmol) in EtOAc (150 mL) at 50°C was added MnO_2 (6.7 g, 76.8 mmol). After stirring for 30 minutes at 50°C more MnO_2 (6.7 g) was added, and 30 minutes later, a third portion of MnO_2 (6.7 g) was added. An hour later, the warm reaction mixture was siltered through celite and the cake was washed with additional EtOAc. Evaporation of the solvents gave the desired aldehyde 5.62 g (83 %).

^1H NMR (CD_3COCD_3): δ 10.4 (1H, s), 7.9 (1H, bs), 7.8 (2H, m), 7.58 (1H, t), 7.38 (1H, bd), 7.1 (3H, m), 4.1 (1H, t), 3.54 (3H, s), 3.13 (1H, ddd), 2.85 (1H, ddd), 2.51 (2H, s), 2.49 (2H, d), 2.2 (2H, m), 1.51 (6H, s), 0.52-0.32 (4H, m).

Step 16: Methyl 1-(((1(R)-((3-(2-(2-thiazolyl)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methyl)-ethyl)phenyl)propyl)thio)methyl)cyclo-propaneacetate

To a suspension of the phosphonium salt from Step 3 (150 mg, 0.38 mmol) in dry THF (3 mL) at -78°C was added BuLi (0.136 mL, 1.6M solution in hexane). The mixture was stirred at -78°C for 1 hr, warmed to -25°C for 30 min and then cooled to -78°C. The aldehyde from Step 14 (104 mg, 0.23 mol) was added. The mixture was stirred at -78°C for 30 min, warmed to 25°C for 15 min. Aqueous NH_4OAc was added and the mixture was extracted with EtOAc. The organic

extract was washed with brine, dried over $MgSO_4$ and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 30% EtOAc in hexane) gave 70 mg (60%) of the title compound.

Step 17: Sodium 1-(((1(R)-((3-(2-(2-thiazolyl)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methyl)-ethyl)phenyl)propyl)thio)methyl)cyclo-propaneacetate

To a solution of the ester of Step 16 in THF (1 mL) and MeOH (1 mL) was added aqueous NaOH (1N, 1.4 mL). The mixture was stirred at 25°C for 20 hr. NH_4Cl was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 20% EtOAc/5% HOAc in hexane) gave 70 mg (95%) of the corresponding acid. To this acid in 3 mL EtOH was added NaOH (1N, 1.0 equivalent). The solvent was evaporated and the product was lyopholysed to give the title compound. Exact mass calculated for $C_{29}H_{33}NO_3S_2Na$ (M+1): 530.1799; found: 530.1797.

EXAMPLE 2

Sodium 1-(((1(R)-((3-(2-(2-(4-isopropyl)thiazolyl)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methyl)ethyl)-phenyl)propyl)thio)methyl)cyclopropaneacetate

Step 1: 1-Bromo-3-methylbutan-2-one

To a solution of 3-methylbutan-2-one (8.5 g, 100 mmol) in MeOH (100mL) at 0°C was added Br_2 (16.9 g, 106 mmol) dropwise. The resulting

mixture was stirred at 10°C for 1 hr. Et_2O (600 mL) was added. The mixture was washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration of the organic extract gave 14 g (85%) of the title compound.

Step 2: 2-Benzoyloxymethyl-4-isopropylthiazole

To a solution of the bromide of Step 1 (14 g, 85 mmol) in toluene (120 mL) was added 2-benzoyloxythioacetamide (21.5 g, 110 mmol) and pyridine (10 mL). The mixture was refluxed for 1 hr. NH_4OAC was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 20% EtOAc in hexane) gave 14 g (63%) of the title compound.

Step 3: 2-Chloromethyl-4-isopropylthiazole

Following the procedure described in Step 2 of Example 1, the title compound was prepared from 2-benzoyloxymethyl-4-isopropythiazole of Step 2 in 85% yield.

Step 4: 2-(4-Isopropyl)thiazolylmethyltriphenyl-phosphonium chloride

Following the procedure described in Step 3 of Example 1, the title compound was prepared from 2-chloromethyl-4-isopropythiazole of Step 3.

Step 5: Sodium 1-(((1(R)-((3-(2-(2-(4-isopropyl)-thiazolyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methyl)ethyl)phenyl)propyl)thio)methyl)-cyclopropaneacetate

Using the procedure described in Steps 4-17 of Example 1, the phosphonium salt of Step 4 was converted to the title compound.

Anal. Calc'd for $C_{32}H_{38}NO_3S_2Na \cdot 3H_2O$:
C, 61.41; H, 7.08; N, 2.23; S, 10.24; Na, 3.67.
Found: C, 61.07; H, 6.55; N, 2.55; S, 10.24; Na, 3.68.

^1H NMR (250 MHz, CD_3COCD_3): δ 0.2-0.6 (4H, m), 1.3 (6H, d), 1.5 (6H, d), 2.0-2.4 (4H, m), 2.6 (1H, m), 2.75 (1H, m), 2.9-3.3 (3H, m), 4.0 (1H, t), 6.9-7.2 (4H, m), 7.25-7.55 (6H, m), 7.65 (1H, s).

EXAMPLES 3-6

Using the methods described above, the compounds of Examples 3-6 were prepared. Analytical data are listed in Table 2.

Table 2

High Resolution Mass Spec. Analysis

Ex	Formula	Calc'd	Found
3	$C_{33}H_{38}NO_3S_2Na + H^+$	584.2269	584.2269
5	$C_{35}H_{42}NO_3S_2Na + H^+$	612.2582	612.2584
8	$C_{33}H_{38}NO_3S_2Na + H^+$	584.2269	584.2270
9	$C_{35}H_{36}NO_3S_2Na + H^+$	606.2113	606.2115
10	$C_{35}H_{35}FNO_3S_2Na + H^+$	624.2018	624.2017
11	$C_{35}H_{35}ClNO_3S_2Na + H^+$	640.1723	640.1724
12	$C_{36}H_{38}NO_4S_2Na + H^+$	636.2218	636.2215

EXAMPLE 7

Sodium 1-(((1(R)-((3-(2-(2-(5-chloro-4-isopropyl)-thiazolyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methyl)-ethyl)phenyl)propyl)thio)methyl)cyclopropaneacetate

Step 1: 5-Chloro-2-chloromethyl-4-isopropylthiazole

To a solution of 2-chloromethyl-4-isopropylthiazole, the title compound of Step 3 of Example 2, (1.36 g, 7.74 mmol) in CCl_4 (2.5mL) was added SO_2Cl_2 (1.15 g, 8.5 mol). The mixture was stirred at 40°C for 1 hr. Ice was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated to an oil. Chromatography of the crude oil on silica gel (eluted with 10% EtOAc in hexane) gave 850 mg (52%) of the title compound.

Step 2:

Using the procedure described in Steps 3-17 of Example 1, the chloride of Step 1 was converted to the title compound.

^{1}H NMR (250 MHz, CD_3COCD_3): δ 0.2-0.5 (4H, m), 1.25 (6H, d), 1.55 (6H, m), 2.0-2.4 (4H, m), 2.75 (1H, m), 3.2 (2H, m), 4.05 (1H, t), 6.9-7.1 (3H, m), 7.2-7.5 (6H, m), 7.65 (1H, s).

EXAMPLES 8-14

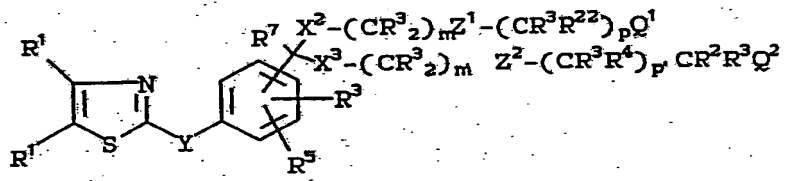
Using the methods described above, the compounds of Examples 8-14 were prepared. Analytical data are listed in Table 2.

EXAMPLES 15-32

Using the methodology of Examples 1-14 and that described in Schemes 1 through 5, the compounds of Examples 15-32 can be prepared.

WHAT IS CLAIMED IS:

1. A compound of the Formula:



I

wherein:

R^1 is H, halogen, CN, lower alkyl, cyloalkyl, polyhalo lower alkyl, lower alkoxy lower alkyl, lower alkoxy, lower alkylthio lower alkyl, substituted or unsubstituted phenylthio lower alkyl, substituted or unsubstituted phenyl, benzyl, pyridyl, thiazolyl, oxazolyl, furanyl or thienyl, or adjacent R^1's and the carbons through which they are attached may form a saturated ring of 5 to 7 carbon atoms;

R^2 is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2CF_3$, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, or two R^2 groups joined to the same carbon may form a saturated ring of up to 8 members containing 0 to 2 heteroatoms chosen from O, S, and N;

R^3 is H or R^2;

CR^3R^{22} may be the radical of a standard amino acid;

R^4 is halogen, $-NO_2$, $-CN$, $-OR^3$, $-SR^3$, NR^3R^3, $NR^3C(O)R^7$, or R^3;

R^5 is H, halogen, $-NO_2$, $-N_3$, $-CN$, $-SR^2$, $-NR^3R^3$, $-OR^3$, lower alkyl, or $-C(O)R^3$;

R^6 is $-(CH_2)_s-C(R^7R^7)-(CH_2)_s-R^8$ or $-CH_2C(O)NR^{12}R^{12}$;

R^7 is H or lower alkyl;

R^8 is A) a monocyclic or bicyclic heterocyclic radical containing from 3 to 12 nuclear carbon atoms and 1 or 2 nuclear heteroatoms selected from N, S or O and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or B) the radical $W-R^9$;

R^9 is contains up to 20 carbon atoms and is (1) an alkyl group or (2) an alkylcarbonyl group of an organic acyclic or monocyclic carboxylic acid containing not more than 1 heteroatom in the ring;

R^{10} is $-SR^{11}$, $-OR^{12}$, or $-NR^{12}R^{12}$;

R^{11} is lower alkyl, $-C(O)R^{14}$, unsubstituted phenyl, or unsubstituted benzyl;

R^{12} is H, R^{11}, or two R^{12} groups joined to the same N may form a saturated ring of 5 or 6 members containing up to two heteroatoms chosen from O, S, and N;

R^{13} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;

R^{14} is H or R^{13};

R^{15} is R^3 or halogen;
R^{16} is H, lower alkyl, or OH;
R^{17} is lower alkyl, lower alkenyl, lower alkynyl, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;
R^{18} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;
R^{19} is lower alkyl, lower alkenyl, lower alkynyl, $-CF_3$, or substituted or unsubstituted phenyl, benzyl, or 2-phenethyl;
R^{20} is H, lower alkyl, substituted or unsubstituted phenyl, benzyl, phenethyl, or pyridinyl, or two R^{20} groups joined to the same N may form a saturated ring of 5 or 6 members containing one to two heteroatoms chosen from O, S, and or N;
R^{21} is H or R^{17};
R^{22} is R^4, CHR^7OR^3, or CHR^7SR^2;
m and m' are independently 0-8;
p and p' are independently 0-8;
m + p is 1-10 when X^2 is O, S, S(O), or $S(O)_2$;
m + p is 0-10 when X^2 is CR^3R^{16} or a bond;
m' + p' is 0-10;
s is 0-3;
Q^1 is $-C(O)OR^3$, 1H (or 2H)-tetrazol-5-yl, $-C(O)OR^6$, $-C(O)NHS(O)_2R^{13}$, $-CN$, $-C(O)NR^{12}R^{12}$, $NR^{21}S(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{21}C(O)R^{18}$, $OC(O)NR^{12}R^{12}$, $-C(O)R^{19}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{12}R^{12}$, $-NO_2$, $NR^{21}C(O)OR^{17}$, $-C(NR^{12}R^{12})=NR^{12}$, or $-C(R^{13})=NOH$; or if Q^1 is C(O)OH and R^{22} is

$-OH$, $-SH$, CHR^7OH or $-NHR^3$, then Q^1 and R^{22} and the carbons through which they are attached may form a heterocyclic ring by loss of water;

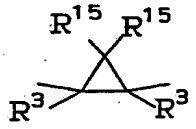
Q^2 is OR^3;

W is O, S, or NR^3;

X^1 is O, S, $-S(O)-$, $-S(O)_2-$, $-N(R^3)-$, or $-CR^3R^3-$;

X^2 and X^3 are independently O, S, S(O), $S(O)_2$, CR^3R^{16}, or a bond;

Y is $-CR^3=CR^3-$, $-C\equiv C-$, $-CR^3R^3-X^1-$, $-X^1-CR^3R^3-$, $-CR^3R^3-X^1-CR^3R^3-$, $-C(O)-$, $-NR^3C(O)-$, $-C(O)NR^3-$, O, S, NR^3, or



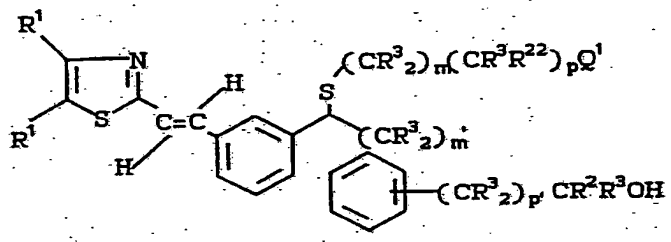
;

Z^1 and Z^2 are independently $-HET(-R^3-R^5)-$ or a bond;

HET is the diradical of a benzene, a pyridine, a furan or a thiophene;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 of the Formula:



Ia

wherein:

R^{22} is R^3, $-CH_2OR^3$, or $-CH_2SR^2$;

Q^1 is $-C(O)OH$, 1H(or 2H)-tetrazol-5-yl, $-C(O)NHS(O)_2R^{13}$, $-C(O)NR^{12}R^{12}$, or $-NHS(O)_2R^{13}$;

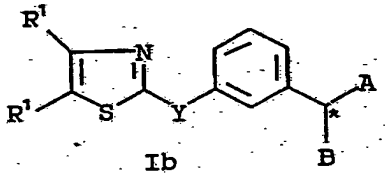
m' is 2 or 3;

p' is 0 or 1; and

m + p is 1-5;

or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 of the Formula:



Ib

wherein the substituents are as follows:

EX. No.	*	R^1	R^1	Y	A	B
1	R	H	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
2	R	4-i-Pr	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
3	R	4-c-Bu	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
4	R	4-c-Pen	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
5	R	4-c-Hex	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
6	R	4-i-Pr	5-Me	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
7	R	4-i-Pr	5-Cl	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
8	R	$-(CH_2)_4-$		CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
9	R	4-Ph	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
10	R	4-(4-F-Ph)	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
11	R	4-(4-Cl-Ph)	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
12	R	4-(4-OMe-Ph)	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$-
13	R	4-c-Pr	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
14	R	4-t-Bu	H	CH=CH	$(CH_2)_2(1,2\text{-phe})C(Me)_2OH$	$SCH_2C(CH_2)_2CH_2CO_2H$
15	R	4-c-Pr	H	CH_2CH_2	$(CH_2)_2(4\text{-Cl-1,2-phe})C(Me)_2OH$	$OCH_2C(CH_3)_2CH_2CO_2H$
16	S	4-t-Bu	5-c-Bu	CH_2O	$(CH_2)_2(4\text{-Cl-1,2-phe})C(Me)_2OH$	$OCH_2CH(CH_3)CH_2T_z$
17	R	4-c-Pen	5-F	$CH(-CH_2-)CH$	$(CH_2)_2(4\text{-F-1,2-phe})C(Me)_2OH$	$SCH_2CH(C_2H_5)CH_2CONMe_2$
18	S	4-Et	5-Me	$CH(CH_3)CH(CH_3)$	$CH_2(4\text{-F-1,2-phe})CMePhOH$	$SCH_2CH_2CO_2H$
19	RS	$4-CH_2Ph$	$5-CF_3$	$CH(-C(CH_3)_2-)CH$	$(CH_2)_2(3\text{-Cl-1,2-phe})CHMeOH$	$SCH_2CH_2CONHS(O)_2Ph$

Ex. No.	*	R^1	R^1	Y	A	B
20	R	4-c-Pr	H	CH_2S	$(CH_2)_2$(5-F-1,2-phe)CMeCF$_3$OH	$SCH_2CH_2CONHS(O)_2CH_3$
21	R	4-PhSCH$_2$	5-Et	$CH(CH_3)CH_2$	(6-CF$_3$-1,2-phe)CHCF$_3$OH	$SCH_2CH_2CONHS(O)_2CF_3$
22	S	$-(CH_2)_3-$		CH=CH	$(CH_2)_2$(4-CF$_3$-1,2-phe)C(CF$_3$)$_2$OH	$SCH_2C(CH_2)_2CH_2CONHS(O)_2Ph$
23	R	4-(2-Fu)	5-F	CH_2CH_2	$(CH_2)_2$(4-F-1,3-phe)CMeEtOH	$CH_2CH_2C(CH_3)_2CO_2H$
24	R	4-(2-Py)	H	CH_2CH_2	$(CH_2)_2$(4-F-1,4-phe)C(CH$_2$)$_2$OH	$SCH_2CH(C_2H_5)Tz$
25	R	4-(2-Th)	H	CH=CH	$(CH_2)_2$(4-F-1,2-phe)C(CH$_2$)$_3$OH	$SCH_2C(CH_2)_2NHS(O)_2CF_3$
26	S	4-CN	H	CH=CH	$(CH_2)_2$(4-F-1,2-phe)C(CH$_2$)$_4$OH	$SCH_2C(CH_2)_3CH_2CO_2H$
27	R	4-CF$_3$	H	CH_2CH_2	$(CH_2)_2$(4-F-1,2-phe)C(CH$_2$)$_5$OH	$SCH_2C(CH_2)_4CH_2CO_2H$
28	S	4-c-Bu	5-OMe	CH_2O	$(CH_2)_2$(2,5-fur)C(Me)$_2$OH	$SCH_2C(CH_2)_5CH_2CO_2H$
29	RS	4-c-Pen	5-Bu	CH(-CH$_2$-)CH	$(CH_2)_2$(1,2-phe)C(Me)$_2$OH	$SCH_2C(CH_3)_2CH_2CO_2H$
30	R	4-c-Hex	H	CH(CH$_3$)CH(CH$_3$)	$(CH_2)_2$(2,5-thio)C(Me)$_2$OH	$SCH_2CH(CH_3)CH_2Tz$
31	R	$-(CH_2)_4-$		CH(-C(CH$_3$)$_2$-)CH	$(CH_2)_2$(2,6-pye)C-(Me)$_2$OH	$SCH_2CH(C_2H_5)CH_2CONMe_2$
32	R	4-c-Bu	H	CH_2S	$(CH_2)_2$(2,4-pye)C(Me)$_2$OH	$SCH_2CH_2CO_2H$

4. A pharmaceutical compositon comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

5. The pharmaceutical composition of Claim 4 additionally comprising an effective amount of a second active ingredients selected from the group consisting of non-steroidal anti-inflammatory drugs; peripheral analgesic agents; cycloxygenase inhibitors; leukotriene antagonists; leukotriene biosynthesis inhibitors; H_1- or H2-receptor antagonists; antihistaminic agents; prostaglandin antoganists; and ACE antagonists.

6. A pharmaceutical composition of Claim 7, wherein the second active ingredient is a non-steroidal anti-inflammatory drug.

7. A pharmaceutical composition of Claim 6, wherein the weight ratio of said compound of Claim 1 to said second active ingredient ranges from about 1000:1 to 1:1000.

8. A method of preventing the synthesis, the action, or the release of SRS-A or leukotrienes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

9. The method of Claim 8 wherein the mammal is man.

10. A method of treating asthma in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

11. The method of Claim 10 wherein the mammal is man.

12. A method of treating inflammatory diseases of the eye in mammal which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

13. A compound of formula (I), or a pharmaceutically acceptable salt, thereof, as defined in Claim 1, 2 or 3, for use in preventing the synthesis, the action, or the release of SRS-A or leukotrienes in a mammal.

14. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in Claim 1, 2 or 3, in the manufacture of a medicament for treating asthma or inflammatory diseases of the eye.

15. A leukotriene antagonist pharmaceutical composition comprising an acceptable leukotriene antagonistic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in Claim 1, 2 or 3, in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 93/00146

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D277/26; C07D277/24; C07D277/64; C07D417/10
A61K31/425

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 318 085 (MERCK FROSST CANADA INC.) 31 May 1989 see claims & US,A,4 962 117 cited in the application	1-15
Y	EP,A,0 219 436 (MITSUBISHI CHEMICAL INDUSTIES LIMITED) 22 April 1987 see claims 1,3,4	1,4-15
Y	GB,A,2 190 377 (MERCK FROSST CANADA INC.) 18 November 1987 see claims 1,6-17	1,4-15

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 JUNE 1993	17. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HENRY J.C.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	CHEMICAL ABSTRACTS, vol. 113, no. 21, 19 January 1990, Columbus, Ohio, US; abstract no. 191338a, page 724 ; see abstract & WO,A,9 006 920 (MITSUBISHI KASEI CORP.) 28 June 1990	1,4-15

INTERNATIONAL SEARCH REPORT

national application No.
PCT/CA93/00146

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-12 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The formulation of claim 1 is so complicated, because of the distinct combinations of the meanings of the variable parts that it does not comply with art. 6 PCT prescribing that the claims shall be clear and concise. For these ~~various~~ reasons the search has been limited to the examples.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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